3. PREVENTION

In deciding when to initiate daily therapy for patients with asthma, clinicians consider the goals of controlling and preventing symptoms, as well as the possibility of preventing further progression of the underlying disease. This section of the EPR Update addresses the question of whether early initiation of daily inhaled corticosteroid treatment is warranted to prevent progression of asthma.

EFFECTS OF EARLY TREATMENT ON THE PROGRESSION OF ASTHMA

Question

For patients with mild or moderate persistent asthma, does early intervention of long-term-control therapy (i.e., inhaled corticosteroids) prevent progression of asthma as indicated by changes in lung function or severity of symptoms?

Summary Answer to the Question

Evidence regarding the benefits of early treatment of asthma in preventing the progression of disease is insufficient to draw conclusions. But available evidence does not support the assumption that children 5 to 12 years of age with mild or moderate persistent asthma experience a progressive decline in lung function (SRE-Evidence A). Further, the evidence indicates that although inhaled corticosteroids provide superior control and prevention of asthma symptoms during treatment of childhood asthma,

Final Daytime Symptom Score	P-Value	Final Nighttime Symptom Score	P-Value	Comments
5.2 (mean; scale, 0–24)				Not sure if reported score is actually a mean; day time score is really overall score where 24 is max and higher value = more asthma symptoms.
3.2 (mean; scale, 0–24)	NS[1]			Not sure if reported score is actually a mean; daytime score is really overall score where 24 is max and higher value = more asthma symptoms.

symptoms and airway hyperresponsiveness worsen when treatment is withdrawn (SRE-Evidence A). This evidence suggests that the therapy controls but does not modify the disease in this age group. Studies in children younger than 3 years of age and in adults document declines in lung function. Studies of whether treatment can prevent these declines in lung function or symptom severity have not yet been conducted in young children and are inconclusive in adults. Revisions to the National Asthma Education and Prevention Program's (NAEPP's) *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma* are recommended to reflect the new understanding of the progression of asthma.

Rationale for the Question

A common question confronting clinicians and patients is: At what point in the disease process—as reflected by the level of clinical signs and symptoms as well the duration of disease—should daily long-term-control therapy be initiated? Although the effectiveness of inhaled corticosteroids in controlling and preventing symptoms of asthma and improving pulmonary function is well documented, an important question is whether inhaled corticosteroids modify the natural history of the disease. If the progression of asthma is from airway inflammation to airway remodeling and some irreversible airway obstruction, then anti-inflammatory medication (i.e., inhaled cortico-steroids) given early in the course of disease may interrupt this process and prevent permanent declines in lung function. In order for early initiation of inhaled cortico-steroids to be more beneficial than delayed initiation, two assumptions must be valid: as a group, people with mild or moderate persistent asthma experience a progressive decline in lung function that is measurable and clinically significant, and treatment with inhaled corticosteroids prevents or slows this decline, in addition to controlling asthma symptoms. A systematic review of the evidence (SRE) was conducted to evaluate the current literature on the effect of intervention of inhaled corticosteroids in altering the progression of disease.

Background Information

Addressing the question about the effect of inhaled corticosteroids on the progression of disease requires answering a series of questions: What is the progression of asthma? Does intervention alter the progression? When is the appropriate time to intervene? The Expert Panel's review of the literature on the progression of asthma is presented here as a context for interpreting the studies evaluated in the SRE.

Natural History of Persistent Asthma

Children

It has been well established that asthma is a variable disease: It can vary among individuals, and its progression and symptoms can vary within an individual's experience over time. It has been postulated that the persistence or increase of asthma symptoms over time is accompanied by a progressive decline in lung function. Recent research suggests that this may not be the case; rather, the course of asthma may vary markedly between young children, older children and adolescents, and adults, and this variation is probably more dependent upon age than symptoms.

A prospective cohort study in which followup began at birth revealed that in children whose asthma-like symptoms began before 3 years of age, deficits in lung growth associated with the asthma occurred by 6 years of age (Martinez et al. 1995). Continued followup on lung function measures taken at 11 to 16 years of age found that compared to the group of children who experienced no asthma symptoms for the first 6 years of life, the group of children whose asthma symptoms began before 3 years of age experienced significant deficits in lung func-

tion at 11 to 16 years of age, but the group whose asthma symptoms began after 3 years of age did not experience deficits in lung function.

A longitudinal study of children 8 to 10 years of age found that bronchial hyperresponsiveness was associated with declines in lung function growth in both children with active symptoms of asthma and children without (Xuan et al. 2000). Thus, symptoms neither predicted nor determined lung function deficits in this age group.

Baseline data from the Childhood Asthma Management Program (CAMP) study support the finding that the individual's age at the time of asthma onset influences declines in lung function growth. At the time of enrollment of children with mild or moderate persistent asthma at 5 to 12 years of age, an inverse association between lung function and duration of asthma was noted (Zeiger et al. 1999). Although the analysis did not distinguish between age of onset and duration of asthma, it can be inferred that because the average duration of asthma was 5 years and the average age of the children was 9 years, most children with the longer duration of asthma started experiencing symptoms before 3 years of age. The data suggest that these were the children with lowest lung function levels. After 4 to 6 years of followup, the children in the CAMP study, on average, did not experience deficits in lung growth (as defined by postbronchodilator FEV_1), regardless of their symptom levels or treatment they received (CAMP 2000).

These results suggest that most of the deficits in lung function growth observed in childhood asthma occur in children whose symptoms begin during the first 3 years of life, and the onset of symptoms after 3 years of age usually is not associated with significant deficits in lung function growth. Further, at least for children with mild or moderate persistent asthma, there do not appear to be deficits in lung function growth from 5 to 17 years of age.

Thus, the most promising target for interventions designed to prevent deficits in lung function and perhaps the development of more severe symptoms later in life would be those children who have symptoms before 3 years of age and are destined to develop persistent asthma. However, it is important to distinguish this group from the majority of children who wheeze before 3 years of age and do not experience any more symptoms after 6 years of age (Martinez et al. 1995). Until recently, no validated algorithms were available to predict which children among those with asthma-like symptoms early in life would go on to have persistent asthma. Data obtained from long-term longitudinal studies of children enrolled at birth generated such a predictive index. This predictive index identified the following risk factors for developing persistent asthma symptoms among children younger than 3 years of age who had more than three episodes of wheezing during the previous year: either physician diagnosis of atopic dermatitis/eczema or a parental history of asthma or two out of three of the following asthma-associated phenotypes-peripheral blood eosinophilia, wheezing apart from colds, or physician-diagnosed allergic rhinitis. When the index was applied to a birth cohort that was followed through 13 years of age, 76 percent of the children who were diagnosed with asthma after 6 years of age had a positive predictive index; moreover, 97 percent of the children in this cohort who did not have asthma after 6 years of age had a negative asthma predictive index before 3 years of age (Castro-Rodriguez et al. 2000).

Adults

Accelerated loss of lung function appears to occur in adults with asthma. In a study of adults with asthma who received 2 weeks of high-dose prednisone if airflow obstruction persisted after 2 weeks of bronchodilator therapy, the degree of persistent airflow obstruction correlated with both the severity and the duration of their asthma (Finucane et al. 1985).

Two large prospective epidemiological studies evaluated the rate of decline in pulmonary function in adults with asthma. In an 18-year prospective study of 66 nonsmokers with asthma, 26 smokers with asthma, and 186 control participants with no asthma, spirometry was performed at 3-year intervals (Peat et al. 1987). Seventy-three percent of the study group underwent at least 6 spirometric evaluations. The slope for decline in lung function (FEV_1) was approximately 40 percent greater for the participants with asthma than for those with no asthma. This did not appear to be the result of extreme measurement produced by a few participants, because fewer than 25 percent of the participants who had asthma were measured with a slope less steep than the mean for those who did not have asthma. In another study, three spirometry evaluations were performed in 13,689 adults (778 who had asthma, 12,911 who did not have asthma) over a 15-year period (Lange et al. 1998). The average decline in FEV_1 was significantly greater in those who had asthma (38 mL per year) than those who did not have asthma (22 mL per year). Although, in this study, asthma was defined simply by patient report, the researchers noted that because the 6 percent prevalence rate for asthma did not increase in this cohort as they increased in age, it is likely that the subjects who reported having asthma did indeed have asthma rather than chronic obstructive pulmonary disease (COPD). It is not possible to determine from these studies whether the loss of pulmonary function occurred in those who had mild or moderate asthma or only in those who had severe asthma. Nevertheless, the data support the likelihood of potential accelerated loss of pulmonary function in adults who have asthma.

Taken together, these longitudinal epidemiological studies and clinical trials indicate that the progression of asthma, measured by declines in lung function, varies in different age groups. Declines in lung function growth observed in children appear to occur by 6 years of age and occur predominantly in those children whose asthma symptoms started before 3 years of age; children 5 to 12 years of age with mild or moderate persistent asthma do not appear to experience declines in lung function through 11 to 17 years of age. There is also evidence of progressively declining lung function in adults.

Data on the effect of interventions to influence the progression of asthma, measured by declines in lung

function, airway hyperresponsiveness, or the severity of symptoms, were evaluated in the SRE.

Systematic Review of the Evidence

Methods of Literature Search

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

In addition to the eligibility criteria for selecting studies related to all topics in the SRE (described in the Introduction), the criteria for selecting studies for this question were as follows:

- (Some or all patients started long-term-control medication (inhaled corticosteroids, leukotriene modifiers, cromolyn, nedocromil, or theophylline) during the study and
  - The treatment group was treated immediately following diagnosis of asthma compared to a control group that received the same treatment after a delay

OR

  - The population was stratified by the duration of asthma prior to the initiation of long-term-control medication and outcomes compared across the different strata.
- Treatment duration was at least 1 year.
- At the start of the study, no more than 10 percent of the population was currently being treated with or had been continuously (more than 1 month) treated in the past with the long-term-control medication being studied.

Summary of Findings

Studies

Although the objective was to review the literature on the effects of any long-term-control medications (e.g., inhaled corticosteroids, leukotriene modifiers, cromolyn, nedocromil, theophylline), the available studies were limited to research on inhaled corticosteroids. (See the key evidence tables in this section for a summary description of the eligible studies.)

Four studies reporting on a total of 475 asthma patients met the inclusion criteria for this key question: two randomized controlled trials (RCTs) (Haahtela et al. 1994; Overbeek et al. 1996) and two single-arm studies (Selroos et al. 1995; Agertoft and Pedersen 1994). Just one of the studies enrolled children who were 3 to 11 years of age (Agertoft and Pedersen 1994). According to EPR-2 classification of severity, two studies involved mild asthma (baseline FEV_1 greater than 80 percent predicted) (Haahtela et al. 1994 and Agertoft and Pedersen 1994), and two involved moderate asthma (Overbeek et al. 1996, Selroos et al. 1995). Each of the two RCTs (Haahtela et al. 1994; Overbeek et al. 1996) was an open-label extension of an RCT originally intended to evaluate the efficacy of inhaled corticosteroids. In these studies, the patients who were initially assigned to the noncorticosteroid-treated control group were subsequently administered inhaled corticosteroids at the conclusion of the original RCT. Each of the single-arm studies (Selroos et al. 1995; Agertoft and Pederson 1944) analyzed a cohort of patients treated in a hospital-based clinic, where the patients were stratified by the individual's duration of asthma prior to initiating inhaled corticosteroids treatment, and outcomes were compared across the strata.

The duration of the followup was 3 years in the randomized trials and 2 and 3.7 years, respectively, in the single-arm studies. Haahtela et al. (1994) treated one group with inhaled corticosteroids for 24 months, then treated the delayed inhaled corticosteroid group for 12 months. Overbeek et al. (1996) treated one group with inhaled corticosteroids for 30 months, initiated treatment with inhaled corticosteroids in the delayed group, and followed both groups for an additional 6 months. In the single-arm studies, patients starting on inhaled corticosteroids were followed for 2 years in one study (Selroos et al. 1995) and for 2 to 6 years (mean: 3.7 years) in the final study (Agertoft and Pedersen 1994).

All four trials reported lung function outcomes, but no two studies used the same measure to report change in lung function from baseline. Neither of the two RCTs (Haahtela et al.; Overbeek et al. 1996) met the SRE criteria that define higher quality studies. Neither study maintained blinding to treatment throughout the course of the study. For both, the rate of dropouts/withdrawals exceeded the established threshold. Analyses were not done by intent to treat or in a manner to minimize dropout bias. With respect to SRE asthma-specific indicators of study quality, both randomized trials established reversibility on lung function measurements and controlled for use of other asthma medications, but neither study reported power calculations for outcomes, adequately accounted for excluded patients, specified a priori which were primary outcomes for analysis, reported compliance, or controlled for the effects of seasonality on outcomes.

A major limitation of the single-arm studies is that patients entered the study at varying time points in the duration of their disease, making it impossible to compare outcome data at a uniform time point. A second limitation in such studies is the high potential for selection bias. It is likely that patients who have had asthma longer will have more severe disease, both because of disease progression and because asthma is more likely to remit in milder cases.

Finally, the SRE literature search found no prospective studies to address this key question in the specific population of interest. As a result, the available evidence from studies that compared early with delayed inhaled corticosteroid treatment has notable limitations with respect to the study population, time frames for study entry and followup, clarity of reporting with respect to details of interest to the question, and the use of appropriate control groups. For some trials, it was impossible to accurately calculate the number of enrolled or evaluable patients of interest, because reporting of one or the other number was combined with other patient groups (e.g., patients who have COPD or individuals with severe asthma).

The SRE also included consideration of results from CAMP 2000, although the research was not published until

after the SRE literature search, and the study design does not address the question of intervention timing (early vs. delayed treatment). The study is considered in the SRE because it evaluates the long-term (4 to 6 years) effect of treatment on lung growth and asthma symptoms in more than 1,000 children with mild or moderate asthma. The RCT comparing inhaled corticosteroids and nedocromil with placebo (all groups received as needed $beta_2$-agonists) met SRE criteria for high quality. Thus, the study provides robust evidence on the course of childhood asthma.

Results of Studies

Of the four studies identified by the SRE literature search, the randomized trial by Haahtela, although small (52 evaluable study participants), is the most relevant in terms of study design and population. The design includes comparisons that directly address the key question of interest, and the population is limited to individuals with mild asthma who were enrolled in the study at a similar point in the history of their disease—i.e., a diagnosis within the 12 months prior to enrollment. The first phase of the study was a randomized control comparison of a group treated daily with inhaled corticosteroids and a group treated with daily $beta_2$-agonists, and followed for 24 months. The second phase of the study was an open-label study in which 67 percent of the original $beta_2$-agonist treatment group was given inhaled corticosteroids and followed for 12 more months; the original inhaled corticosteroid treatment group was either continued on a reduced dose of steroid or given a placebo. Outcomes at the end of 3 years indicated improvements in lung function measures and symptom scores in both groups, with larger increases occurring in the immediate inhaled corticosteroid group compared to the delayed inhaled corticosteroid group (FEV_1 0.15L vs. 0.02 L; PEF 42L/min vs. 15 L/min; PC15 5.0 vs. 4.22 DD histamine; symptom score change of 0.8 vs. 0.4 from a mean baseline of 2.2 on a 1 to 10 point scale). Although these findings appear to support the hypotheses that an irreversible decline in lung function can occur in asthma not treated with an anti-inflammatory medication and that treatment with inhaled corticosteroids may have an impact on decline, methodologic features of the study limit the conclusions that can be reached. No statistical tests of significance were performed comparing baseline and 3-year outcomes between the immediate and the delayed treatment groups, and the differences are of unknown clinical significance because the magnitude is of a size that could be explained by bias. Bias may have occurred due to the lack of strict comparability between the double-blind and open-label phases of the trial, lack of controls for doses of inhaled corticosteroids, and a high rate of withdrawal from the study during the open-label phase (36 of 53 patients in the delayed treatment group and 16 of 50 in the immediate treatment group were available for analysis at 3 years), with no tests of comparability between withdrawals and continuing patients.

The second randomized trial identified in the SRE is also an open-label extension of a double-blind RCT designed to evaluate the efficacy of inhaled corticosteroids. The study had three treatment groups: one received inhaled corticosteroids, a second received inhaled ipratropium, and a third received placebo, but all groups received an inhaled $beta_2$-agonist four times a day (Overbeek et al. 1996). After 30 months of treatment, the asthma patients in the groups not receiving inhaled corticosteroids were given that agent and followed 6 additional months in an open-label observation. This allows comparison of a group (49 patients) receiving immediate vs. a group (53 patients) receiving delayed inhaled corticosteroids for asthma. Results reported a greater but not statistically significant rise in FEV_1 during the initial 3 months of inhaled corticosteroid therapy for the immediate treatment group (13.8 percent increase vs. 8.5 percent increase; $p = 0.13$), and a statistically significant rise in PC15 values for the initial 6 months of inhaled corticosteroids in the immediate treatment group (1.77 doubling dose vs. 0.79, $p = 0.03$), and no differences in symptom score values. The study suggests the possibility of some benefit for immediate treatment, but conclusions are severely limited by several methodologic problems. For example, it is not clear at what point in the individual patient's disease process the treatment was started; the study populations include a mix of patients with severe asthma and COPD, and there were no comparisons made relevant to the key question—i.e., comparison of baseline and final lung function measured at the end of the trial. Further, there was a high dropout rate (less than half the eligible patients participated in the extended open-label phase) with no analysis of the withdrawals, which may introduce bias.

For the single-arm studies, one study enrolled 105 consecutive patients started on inhaled corticosteroids and observed them for 2 years (Selroos 1995). Changes in lung function outcomes (FEV_1 percent predicted and peak expiratory flow [PEF] percent predicted) were compared among the patients, according to groups stratified by duration of asthma at the onset of treatment (0 to 6 months, 14 patients; 6 to 12 months, 35 patients; 12 to 14 months, 13 patients; 24 to 60 months, 19 patients; 60 to 120 months, 15 patients). All strata were compared to the 0-to-6 month duration group; no comparison among strata was reported. The greatest increase in lung function measures occurred in the group with the shortest (0 to 6 months) duration of asthma (17 percent increase in FEV_1 percent predicted); and the least increase occurred in the group with the longest (60 to 120 months) duration of asthma (0 percent increase, $p < 0.01$). All other strata except the 24-to-60-month group had significantly less degree of lung function improvement than the 0-to-6-month group, but of varying magnitude. For PEF, the 0-to-6-month group had a 21 percent increase in percent predicted values, compared with a 2 percent increase in the 60-to-120-month group ($p < 0.05$), but differences among the other strata varied in magnitude and significance. Although the stratification accounted for differences in duration of disease, it is impossible to compare outcome data at a uniform time point in the disease. Further, baseline differences in lung function and asthma

severity indicate some selection bias. Finally, approximately one-third of the study participants were current or exsmokers, and the proportion of current smokers varied from 0 percent to 29 percent in the different groups. Thus, study design features, variance in final outcome measures among the strata, and the confounding factors of asthma severity and smoking limit interpretation of the results.

The second single-arm study identified by the SRE is a nonrandomized, prospective controlled trial of long-term outcomes in 216 children treated with inhaled corticosteroids for a mean of 3.7 years compared to 62 children who declined recommendations for inhaled corticosteroid treatment (Agertoft and Pedersen 1994). In a supplemental cohort analysis, patients in the inhaled corticosteroid group were stratified by prior duration of asthma (0 to 2 years, 2 to 3 years, 3 to 5 years, and more than 5 years). This allowed a comparison relevant to the key SRE question. The main reported outcome was annual change in percent predicted FEV_1, calculated by linear regression. Results showed a mean change in FEV_1 per year of 8.2 percent for the 0-to-2-year group, 6.7 percent for the 2-to-3-year group, 3 percent for the 3-to-5-year group, and 2.4 percent for the more than 5-year group. A statistically significant correlation existed between the duration of asthma and the estimated change in FEV_1 per year, however the differences were not significant between every group (e.g., the less than 2 vs. the 2-to-3-year strata or the 3-to-5-year vs. the more than 5-year strata). A major difficulty in interpreting these results is that the linear regression assumes a linear change in outcomes over the entire course of the study. However, it is well documented in the literature that there is a pattern of a sharp initial rise in FEV_1 during the first 3 months of inhaled corticosteroid treatment that is then followed by a plateau. Indeed, the final difference in FEV_1 percent predicted between the less than 2-year strata (101 percent) and the more than 5-year strata (96.2 percent) was 4.8 percent after a mean of 3.7 years of treatment. This is considerably less than the 5.8 percent per year difference estimated by the linear regression model applied to the data.

The results of the CAMP 2000 study influence the conclusions derived from the SRE (CAMP 2000). This study is a three-arm, RCT evaluating the outcome effects of inhaled corticosteroids or nedocromil sodium compared to placebo in 1,041 children over a mean followup period of 4.3 years. The primary outcome measure was postbronchodilator FEV_1. Although the design of CAMP does not address the question of early versus delayed intervention (the average duration of asthma was 5 years for the study population), it does address the question of the effect of intervention with two treatments on disease progression as defined by loss in FEV_1 percent predicted.

CAMP researchers found an initial, highly statistically significant difference between treatment and control groups for change in postbronchodilator FEV_1 in the first year of the study, but no difference in change from baseline to the end of the 4-to-6-year followup period. This outcome measure was chosen to minimize the effects of reversible airway constriction and individual variability over time that are observed with prebronchodilator FEV_1. The finding of no difference in postbronchodilator FEV_1 and minimal change overall in lung function over 4 to 6 years for the entire study population does not support the hypothesis that treatment with inhaled corticosteroids improves lung growth in children with mild or moderate persistent asthma. It is of particular interest that CAMP does not document progressive decline in lung function in the placebo group, or significant improvement from baseline in the treatment groups (CAMP 2000). Similar to the findings related to lung function outcomes, no progressive decline in symptoms with the placebo groups was noted. Symptom scores and night-awakening scores improved over the course of the study in both the inhaled corticosteroid and placebo groups, with greater improvement throughout the study period shown in the inhaled corticosteroid group. The improvements in the placebo group may have been a result of the close medical supervision and patient education given to all study participants, but the greater improvements in symptom scores and airway hyperresponsiveness indicate superior effectiveness of inhaled corticosteroid treatment. However, after inhaled corticosteroid treatment was withdrawn, symptom scores and airway hyperresponsiveness values were no different between groups. This finding indicates that the inhaled corticosteroids provided superior control and prevention of symptoms, but did not modify underlying disease. The finding that the placebo group did not experience a decline in lung function does not support the assumption of such a decline in children with mild or moderate asthma in this age group.

As noted in the Background Information section, it is likely that a progressive decline in lung function occurs in younger children and in adults. It is also possible it occurs in individuals with more severe asthma.

The studies identified by the SRE most relevant to addressing the question of whether early intervention with inhaled corticosteroids can prevent progression of disease were suggestive of benefit, but methodologic issues severely limit the conclusions that may be drawn. Additional consideration of the CAMP study supports cautious interpretation of the studies identified in the SRE. Although none of these studies was designed specifically to compare immediate versus delayed treatment in preventing progression of disease, the results provide critical insights for future research. At this time, the Expert Panel concludes that the evidence is insufficient to permit conclusions regarding the use of early intervention vs. long-term-control medication to prevent progression of disease.

Recommendations for EPR Update

Modifications in the EPR-2 are necessary to reflect the current understanding of natural history of persistent asthma, based on the SRE and review of additional, recently published studies that provide insights on the progression of asthma. It is clear that further research is needed to define the benefits of early intervention, the appropriate time of intervention, the nature of asthma as

a progressive disease, and the effect of medications on preventing progression. Until this information is available, the Expert Panel recommends the following revisions to EPR-2 (noted by shaded text), based on the SRE.

Introduction: Pharmacologic Therapy (page 4, column 2, final paragraph in EPR-2)

Observations into the basic mechanisms of asthma have had a tremendous influence on therapy. Because inflammation is considered an early and persistent component of asthma, therapy for persistent asthma must be directed toward long-term suppression of the inflammation. Thus, EPR-2 continues to emphasize that the most effective medications for long-term-control are those shown to have anti-inflammatory effects. For example, early intervention with inhaled corticosteroids can improve asthma control and normalize lung function. However, it remains to be determined whether intervention with inhaled corticosteroids or any other long-term-control therapy can prevent irreversible airway obstruction that may be associated with asthma (Evidence D).

Pathogenesis and Definition: Child Onset Asthma (page 10, column 1, paragraph 2 in EPR-2)

Asthma often begins in childhood, and when it does, it is frequently found in association with atopy, which is the genetic susceptibility to produce IgE directed toward common environmental allergens, including house-dust mites, animal proteins, and fungi (Larsen 1992). With the production of IgE antibodies, mast cells and possibly other airway cells (e.g., lymphocytes) are sensitized and become activated when they encounter specific antigens. Although atopy has been found in 30 to 50 percent of the general population, it is frequently found in the absence of asthma. Nevertheless, atopy is one of the strongest predisposing factors in the development of asthma (Sporik et al., 1990). Furthermore, a large epidemiologic study shows that among children who have recurrent episodes of wheezing during the first 3 years of life and have either one of two major risk factors (parental history of asthma or physician diagnosis of atopic dermatitis) or two of three minor risk factors (wheezing apart from colds, peripheral blood eosinophilia, or physician diagnosis of allergic rhinitis) have a 76 percent probability of developing asthma during the school years (Evidence C) (Castro-Rodriguez et al. 2000).

Pathogenesis and Definition. Airway Remodeling (page 11, column 2, paragraph 3 in EPR-2)

Airway remodeling. In some patients with asthma, airflow limitation may be persistent and nonresponsive to treatment. This nonresponsiveness may be caused by changes in the structure of airways. These changes include wall thickening, subepithelial fibrosis, goblet cell hypermetaplasia, myofibroblast hyperplasia, myocyte hyperplasia and hypertrophy, vascular neogenesis, and epithelial hypertrophy (Elias 1999). Regulation of the repair and remodeling process is not well established, but both the process of repair and its regulation are likely to be key events in explaining the persistent nature of the disease and limitations to a therapeutic response. Although yet to be fully explored, the importance of airway remodeling as a possible cause of persistent airflow limitation and the possible role of chronic inflammation as a cause of remodeling suggest a rationale for early intervention with anti-inflammatory therapy. This hypothesis must be confirmed with specific, prospective, controlled studies.

Component 1: Measures of Assessment and Monitoring. Spirometry (page 28, column 1 in EPR-2)

The Expert Panel recommends that spirometery tests be done (1) at the time of initial assessment; (2) after treatment is initiated and symptoms and peak expiratory flow (PEF) have stabilized, to document attainment of (near) "normal" airway function; and (3) at least every 1 to 2 years to assess the maintenance of airway function. These spirometry measures should be followed over the patient's lifetime to detect potential for decline and rate of decline of pulmonary function over time (Evidence D).

Component 3: Pharmacologic Therapy. Key Points: The Medications, Inhaled Corticosteroids (page 58 in EPR-2)

Increased understanding of inhaled corticosteroids notes that:

– Early intervention with inhaled steroids likely will improve overall asthma management, but its effect on preventing irreversible airway injury remains to be determined (SRE-Evidence A, B).

Component 3: Pharmacologic Therapy. Special Considerations for Managing Asthma in Different Age Groups. Infants and Young Children, Diagnosis (page 95, column 1, paragraph 2 in EPR-2)

Among children 5 years of age and younger the most common cause of asthma symptoms is viral respiratory infection. At present, the relative contributions of airway inflammation, bronchial smooth muscle abnormalities, or other structural factors in producing wheeze with acute viral upper respiratory infections are unknown. There appear to be two general patterns of illness in infants and children who have wheezing with acute viral upper respiratory infections: a remission of symptoms in the preschool years and persistence of asthma throughout childhood.

No clear markers to predict the prognosis for an individual child exist. However, epidemiologic studies suggest that for children less than 3 years of age who have more than 3 episodes of wheezing in a year (that last more than 1 day and affect sleep), the following predictive index identifies the risk associated with persistent asthma after 6 years of age. If a child has either (a) a physician diagnosis of atopic dermatitis or a parental history of asthma OR (b) two of the following: physician-diagnosed allergic rhinitis, greater than 4 percent peripheral blood eosinophilia, or wheezing apart from colds, then the child has a high likelihood (76 percent probability) of developing persistent asthma (Evidence C) (Martinez 1995; Cas-

tro-Rodriguez 2000). It is conceivable that early recognition and treatment of these high-risk children could result in secondary prevention of persistent asthma, although this is not yet established by clinical trials.

Component 3: Pharmacologic Therapy, Special Considerations for Managing Asthma in Different Age Groups. Infants and Young Children, Treatment (page 95, column 2 in EPR-2)

In deciding when to initiate daily long-term-control therapy, the clinician must weigh the possible long-term effects of inadequately controlled asthma vs. the possible adverse effects of medications given over prolonged periods. There is evidence that anti-inflammatory treatment can reduce morbidity from wheezing in early childhood (Connett et al. 1993). Long-term studies in children 5 to 12 years of age at the time of enrollment conclude that inhaled corticosteroids improve health outcomes for children with mild or moderate persistent asthma and that the potential albeit small risk of delayed growth from the use of inhaled corticosteroids is well balanced by their effectiveness (SRE-Evidence A) (CAMP 2000). Further, available long-term data indicate that most children treated with inhaled corticosteroids achieve their predicted adult heights (Agertoft and Pedersen 2000). It is noted that the long-term prospective studies on growth involved budesonide and that the retrospective analyses included studies on beclomethasone, but the results have been generalized to include all inhaled corticosteroid preparations. Although different preparations and delivery devices may have a systemic effect at different doses, all short-term studies of numerous preparations suggest that the potential effect of inhaled corticosteroids on growth is a drug class effect. In children with demonstrable adverse effects related to inhaled corticosteroid therapy, other options (cromolyn, LTRA, nedocromil, or theophylline) for initiating or maintaining long-term-control therapy are available.

Based on high-quality evidence, the Expert Panel recommends long-term-control therapy for children with mild or moderate persistent asthma because it controls and prevents asthma symptoms (SRE Evidence A). However, evidence to date is insufficient to permit conclusions regarding whether early vs. delayed intervention with daily long-term-control medication will alter the underlying course of the disease. Although a preliminary study suggests that appropriate control of childhood asthma may prevent more serious asthma or irreversible obstruction in later years (Agertoft and Pedersen 1994), these observations were not verified in a recent long-term RCT in children 5 to 12 years of age (CAMP 2000) (SRE-Evidence A, B). The best available evidence does not support the assumption that children 5 to 12 years of age with mild or moderate persistent asthma have a progressive decline in lung function that can be prevented by early initiation of long-term-control medications. Observational prospective data from other large groups of children suggest that the timing of the CAMP intervention was too late, as most loss of lung function in childhood asthma appears to occur in the first 3 to 5 years of life (Martinez et al. 1995). However, it has not yet been determined whether early recognition of children at high risk of developing persistent asthma coupled with early therapeutic intervention will either prevent the loss of lung function or prevent the development of persistent disease. Currently, critical prospective studies to address these issues are in progress. Similarly, to date no studies have evaluated whether intervention with inhaled corticosteroids can prevent the more rapid decline in lung function that can occur in adults with asthma.

Recommendations for Future Research

The SRE revealed methodological problems in most of the studies that evaluated the effect of inhaled corticosteroids on the progression of asthma. RCTs designed explicitly to address the research question are urgently needed. Further, new opportunities are now available to treat children younger than 5 years of age in whom the incidence of asthma onset is highest (Yuninger et al. 1992) and the risk for declines in lung function growth are high (Stern 2000, Castro-Rodriquez 2000). For example, leukotriene receptor antagonist (LTRA) is available for children as young as 2 years of age and inhaled corticosteroid nebulizing suspension for children as young as 1 year of age. In addition, new classes of medication that may be feasible for young children currently are being evaluated for their potential to modify disease: e.g., anti-IgE agents, cytokine antagonists, and cytokine receptor antagonists.

Because disease onset is high in children younger than 5 years of age and because these children are initially evaluated and managed by primary care physicians, it is important to establish firm diagnostic criteria for persistent asthma. Further, a refinement in the definition of disease progression must occur and methods to monitor progression should be designed and evaluated for use in clinical practice.

Specifically, more information in the following areas is needed to enhance our knowledge about the natural progression of asthma in children and adults, as well as appropriate interventions to alter it:

- Additional long-term studies, lasting a minimum of 2 years, of each medication class (e.g., inhaled corticosteroids, LTRAs, anti-IgE) in order to define the impact of treatment on the progression of asthma. Studies should:
  - In young children, be designed to assess for effect on measures including pulmonary function
  - In adults, be designed to examine whether loss of pulmonary function may be a unique feature of adult asthma, especially adult-onset asthma.
- Studies to determine the significance of declines in lung function and its relevance to other long-term events, including quality of life and severity of symptoms (acute exacerbations, symptoms, nighttime awakenings). Identification of the most appropriate pulmonary function measure to use for monitoring lung function growth in children and lung function declines in adults.
- Studies to identify the prevalence of airway remodeling and whether it can be predicted by asthma phenotype and genotype.

- Studies to identify methods for reliably and easily measuring and interpreting pulmonary function in young children. Forced oscillation could improve the feasibility of pulmonary function testing in young children, but these tests must be verified.
- Validation of a profile to predict persistent asthma and levels of asthma severity.
- Studies to identify and compare relevant outcomes that define disease progression and measure the effects of interventions to alter it. Pulmonary function, airway hyperresponsiveness, markers of inflammation, symptoms, medication use, and disease severity classifications are some outcomes of interest.
- Studies to design and evaluate methods for use in primary clinical practice to monitor individuals for progression of their disease. Serial measures of pulmonary function, assessments of medication requirements and urgent care visits over time, and, for infants, application of the asthma predictive index are possible approaches.
- Studies to evaluate when long-term-control therapy might be discontinued.
- Studies to evaluate the effectiveness of early use of environmental control measures, with or without pharmacologic therapy, alter the progression of disease.

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Key Evidence Tables

TABLE 3–1. Study Characteristics

Citation	Study Design	Study Setting
Overbeek, Huib, Kerstjens, et al., 1996	Open label extension of randomized parallel arm, double-blinded, placebo controlled trial	Country: Netherlands Funding: Pharm + gov't grant Tx Setting: Unknown/Other; Multicenter
Haahtela, Jarvinen, Kava, et al., 1994	Open label extension of randomized parallel arm, double-blinded, controlled trial	Country: Scandinavia Funding: Not specified Tx Setting: Unknown/Other; Multicenter
Agertoft and Pedersen, 1994	Prospective cohort analysis within parallel, controlled trial; patients stratified by prior duration of asthma	Country: Scandinavia Funding: Not specified Tx Setting: Unknown/Other
Selroos, Pietinalho, Lofroos, et al., 1995	Prospective cohort study; patients stratified by prior duration of asthma	Country: Scandinavia Funding: Not specified Tx Setting: Unknown/Other

Source: Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

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Asthma Severity	Eligibility
Stated: Not specified	Patient eligibility based on lung function only.
Estimated: Unable to estimate	(1) FEV_1 (type not specified) minimum 1.2 L and 1.64 to 4.5 residual SDs below predicted, or FEV_1/inspiratory vital capacity ratio >1.64 residual SDs below predicted. (2) Histamine PC20 maximum 8 mg/mL. Exclusions: Patients with medication use or conditions likely to interfere with the purpose of the study.
Stated: Mild	Patient eligibility based on lung function and symptoms.
Estimated: Mild	FEV_1 (postdose) minimum 80% of predicted; increase of more than 15% after inhalation of $beta_2$-agonist or decrease of more than 15% after exercise tolerance test. Maximum duration of symptoms 12 months. Exclusions: History of smoking within 6 months, regular asthma treatment, prior treatment with corticosteroids or cromolyn.
Stated: Mild-moderate	Patient eligibility based on utilization and stated severity.
Estimated: Mild-Severe	Minimum of three prior visits to clinic within past year, with mild or moderate persistent asthma. Exclusions: Prior use of inhaled corticosteroids for more than 2 weeks per year; other chronic diseases.
Stated: Mild-moderate	Patient eligibility based on lung function and symptoms.
Estimated: Mild-Severe	FEV_1 (type not specified) maximum 75% of predicted or PEF (a.m. clinic) maximum 75% of predicted; and/or use of inhaled bronchodilators >3x/week, and/or regular asthma symptoms during day or night, and/or reduced exercise tolerance. Exclusions: Prior use of inhaled corticosteroids; irreversible airway obstruction.

TABLE 3–2. Study Parameters

Citation	Pretreatment	Study Arm	Number Enrolled
Overbeek, Huib, Kerstjens, et al., 1996	None	Inhaled corticosteroid—immediate	
		Inhaled corticosteroid—delayed	
Haahtela, Jarvinen, Kava, et al., 1994	Run-in 2 weeks to establish patient eligibility	Inhaled corticosteroid—immediate	
		Inhaled corticosteroid—delayed	
Agertoft and Pedersen, 1994	Run-in 52 weeks to establish patient eligibility	Inhaled corticosteroid—immediate	
		Inhaled corticosteroid—delayed 1	
		Inhaled corticosteroid—delayed 2	
		Inhaled corticosteroid—delayed 3	
Selroos, Pietinalho, Lofroos, et al., 1995	None	Inhaled corticosteroid—immediate	
		Inhaled corticosteroid—delayed 1	
		Inhaled corticosteroid—delayed 2	
		Inhaled corticosteroid—delayed 3	
		Inhaled corticosteroid—delayed 4	
		Inhaled corticosteroid—delayed 5	

Source: Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Corticosteroid Delay	Treatment
Corticosteroids delayed 0 months, then administered for 36 months	All patients received 200 mcg beclomethasone dipropionate 4x daily; all patients received 500 mcg terbutaline 4x daily.
Corticosteroids delayed 30 months, then administered for 6 months	All patients received 500 mcg terbutaline 4x daily for entire study. Some patients received 40 mcg ipratropium bromide 4x daily for first 30 months of study. All patients received 200 mcg beclomethasone dipropionate 4x daily for final 6 months of study.
Corticosteroids delayed 0 months, then administered for 36 months	All patients received 600 mcg budesonide 2x daily for first 24 months, then reduced to 200 mcg 2x daily for final 12 months of study.
Corticosteroids delayed 24 months, then administered for 12 months	All patients received 600 mcg budesonide 2x daily for final 12 months of study.
Prior duration of asthma 0–12 months; inhaled corticosteroids administered for at least 24 months	All patients received 800 mcg budesonide daily (frequency of dosing not specified).
Prior duration of asthma 12–24 months; inhaled corticosteroids administered for at least 24 months	All patients received 800 mcg budesonide daily (frequency of dosing not specified).
Prior duration of asthma 24–36 months; inhaled corticosteroids administered for at least 24 months	All patients received 800 mcg budesonide daily (frequency of dosing not specified).
Prior duration of asthma 12–24 months; inhaled corticosteroids administered for at least 24 months	All patients received 800 mcg budesonide daily (frequency of dosing not specified).
Prior duration of asthma 0–6 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.
Prior duration of asthma 6–12 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.
Prior duration of asthma 12–24 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.
Prior duration of asthma 24–60 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.
Prior duration of asthma 60–120 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.
Prior duration of asthma >120 months; inhaled corticosteroids administered for 24 months	Average daily dose for entire population 454 mcg budesonide 2x daily at start of study; 374 mcg 2x daily after 2 years of treatment.

TABLE 3–3. Lung Function Outcomes: FEV_1

Citation	Study Arm	Number Enrolled	Number Evaluable	Study Duration (years)	FEV_1 Baseline
Overbeek, Huib, Kerstjens, et al., 1996	Inhaled corticosteroid—immediate	91	49	3.0	64.6 +/- 14.1% predicted
	Inhaled corticosteroid—delayed	183	53	3.0	61.2 +/- 15.6% predicted
Haahtela, Jarvinen, Kava, et al., 1994	Inhaled corticosteroid—immediate	50	16	3.0	3.17 +/- 0.8 L
	Inhaled corticosteroid—delayed	53	36	3.0	3.05 +/- 0.7 L
Agertoft and Pedersen, 1994	Inhaled corticosteroid—immediate			3.7	NR
	Inhaled corticosteroid—delayed 1			3.7	NR
	Inhaled corticosteroid—delayed 2			3.7	NR
	Inhaled corticosteroid—delayed 3			3.7	NR
Selroos, Pietinalho, Lofroos, et al., 1995	Inhaled corticosteroid—immediate	14		2.0	70 +/- 21% predicted
	Inhaled corticosteroid—delayed 1	35		2.0	70 +/- 21% predicted
	Inhaled corticosteroid—delayed 2	13		2.0	78 +/- 18% predicted
	Inhaled corticosteroid—delayed 3	19		2.0	60 +/- 16% predicted
	Inhaled corticosteroid—delayed 4	15		2.0	62 +/- 18% predicted
	Inhaled corticosteroid—delayed 5	9		2.0	67 +/- 21% predicted

Source: Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01–EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

FEV_1 Final	FEV_1 P-Value	Comments
13.8% pred (change, 95% CI, 7.7–18.7)		Number of patients enrolled includes both COPD and asthma patients; number evaluable includes only asthma patients.
8.5% pred (change, 95% CI, 3.3–15.9)	NS	Comparison only made of rise in FEV_1 during initial 3 months' treatment with inhaled corticosteroids in both groups.
3.32 L		Values represent FEV_1 at start of initial study and final FEV_1 after 3 years.
3.07 L		No statistical comparison performed on change in FEV_1 from start of study until final end-point.
8.2% pred/yr (change, 95% CI, 6.1, 10.3)		Final FEV_1 % predicted 101 +/- 13.6% Calculation of % increase/yr in FEV_1 by linear regression probably not appropriate.
6.7% pred/yr (change, 95% CI, 5.0, 8.4)		
3% pred/yr (change, 95% CI, 1.8, 4.2)		
2.4% pred/yr (95% CI, 1.1, 3.7)		Final FEV_1 % predicted 96.2 +/- 9.5%, $p < 0.05$ as compared to inhaled corticosteroid-immediate group.
87 +/- 18.7% predicted		
75 +/- 17.7% predicted	.0100	Comparison of change in FEV_1 vs. Ctl
85 +/- 18.0% predicted	<.0500	Comparison of change in FEV_1 vs. Ctl
68 +/- 21.8% predicted	NS	Comparison of change in FEV_1 vs. Ctl
66 +/- 19.4% predicted	<.0500	Comparison of change in FEV_1 vs. Ctl
67 +/- 30.0% predicted	<.0100	Comparison of change in FEV_1 vs. Ctl